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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,030	10/24/2003	Matthias H. Kraus	14014.0306U2	2346

36339 7590 06/11/2008

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EXAMINER	
GODDARD, LAURA B	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
06/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,030	KRAUS ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-79* is/are pending in the application.

4a) Of the above claim(s) *35-42,47-50 and 60-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-46 and 51-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed January 7, 2008 in response to the Office Action of July 6, 2007, is acknowledged and has been entered. Claims 35-79 are pending. Claims 60-79 are new. Previously pending claims 43 and 47 have been amended. Claims 35-42 and 47-50 remain withdrawn.

Newly submitted claims 60-79 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The new claims are drawn to methods of determining the level of expression of erbB-3 in a sample and assay for detection of the level of expression of erbB-3 in a biological sample. These methods are distinct from the elected and examined invention of classifying a cancer as being correlated with a greater amount of expression of an erbB-3 gene as compared to a control. The newly claimed invention and the elected invention are drawn to materially distinct methods which differ at least in objectives, method steps, response variables, and criteria for success. Furthermore, there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 60-79 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 43-46 and 51-59 are currently being examined.

Priority

2. The prior Office Action, mailed July 6, 2007 stated on pages 2-4, sections 2 and 3:

> 2. It is noted that the preliminary amendment filed in this case on October 24, 2003, but not referred to in the executed Declaration as originally filed, is not considered to be part of the original disclosure because the MPEP specifically states that "For applications filed on or after September 21, 2004 (the effective date of 37 CFR 1.115(a)(1)), a preliminary amendment that is present on the filing date of the application is part of the original disclosure of the application. For applications filed before September 21, 2004, a preliminary amendment that is present on the filing date of the application is part of the original disclosure of the application if the preliminary amendment was referred to in the first executed oath or declaration under 37 CFR 1.63 filed in the application. See MPEP § 602." Please review MPEP 714.01 (e). However, a review of the Declaration does not reveal any reference to the preliminary amendment filed on October 24, 2003. The preliminary amendment is drawn to a method of classifying a cancer as being correlated with expression of an erbB-3 gene. However, the preliminary amendment as filed contains subject matter not otherwise included in the specification and drawings of the application since neither the term "classifying" nor the concept of classifying a cancer as being correlated with expression of an erbB-3 gene is found in the specification as originally filed. It is further noted that if the amendment had been filed on any date other than the date that the application was filed, claims drawn to said subject matter would be rejected under the new matter provisions of 35 USC 112, first paragraph.
>
> Since the preliminary amendment contains subject matter not otherwise included in the specification and drawings of the application as set forth above, Examiner is requiring applicant to provide a supplemental oath or declaration under 37 CFR 1.67 referring to such preliminary amendment. It is further noted that the failure to submit a supplemental oath or declaration under 37 CFR 1.67 referring to a preliminary amendment that contains subject matter not otherwise included in the specification or drawings of the application as filed removes safeguards that are implied in the oath or declaration requirements that the inventor review and understand the contents of the application, and acknowledges the duty to disclose to the Office all information known to be material to patentability as defined in 37 CFR 1.56. In response to this requirement, applicant must submit (1) an oath or declaration that refers to the preliminary amendment, (2) an amendment that cancels the subject matter not supported by the originally filed specification and drawings, or (3) a request for reconsideration. Please review MPEP 714.01 (e).

Further, upon submission of the substitute oath or declaration, it is noted that the specification will be objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Because the claims as filed in the original specification are part of the disclosure, even though the material disclosed in the claims is not disclosed in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. In re Benno, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985). Thus amendment of the specification to include the material disclosed in the claims would obviate this objection.

Finally, it is further noted that, given that the preliminary amendment is drawn to subject matter not otherwise included in the specification and drawings of the application as set forth above, the instant application is not in fact a divisional application of the parent application, but rather a continuation-in-part of the parent application and the supplemental oath filed must include an acknowledgement of the duty to disclose to the Office all information known to be material to patentability as defined by 35 CFR 1.56.

3. In view of the preliminary amendment, Examiner has established a priority date of October 24, 2003 for the instantly claimed invention. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date October 24, 2003 for the instantly claimed invention, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Should Applicants successfully argue against the priority date established by Examiner, Examiner further notes that the instant application claims priority to Application 07/978,895, now US Patent 5,480,968, filed 11/10/1992, which is a CIP of Application 07/444,406, now US Patent 5,183,884, filed 12/1/1989. Examiner notes that Application 07/444,406 does not provide support for the elected invention of the instant application, therefore the instantly examined claims do not receive priority to Application 07/444,406. There is no disclosure in Application 07/444,406 of a method of classifying a cancer as being correlated with a greater amount of expression of an erbB-3 gene as compared to a control comprising measuring the level of expression of erbB-3 gene in a

sample from a subject diagnosed with cancer and comparing the level of expression to the level of expression in a sample form a control subject. Therefore, if Applicants successfully argue against the priority date established by Examiner, there is still no support for the elected invention in Application 07/444,406 , therefore the examined claims do not receive the priority date of the Application 07/444,406.

Applicants did not argue or address the priority issues presented by Examiner above, therefore Examiner maintains a priority date of October 24, 2003 for the instantly claimed invention.

Specification

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). Specifically, **there are no SEQ ID NOs identified with the sequences disclosed in Figures 3 and 4.** If these sequences were not already submitted, Applicant is required to provide (1) a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, (2) a substitutes paper copy of the "Sequence Listing", (3) an amendment directing the entry of that paper into the specification, and (4) a statement that the content of the paper and computer readable copies are the same, **and, where applicable, include no new matter, as required by CFR 1.821(d) which requires a reference to a particular sequence identifier (i.e.,**

SEQ ID NO:#) be made in the specification and claims wherever a reference is made to that sequence (See MPEP 2422.04).

New Rejections

(based on new considerations)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 43-46 and 51-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a method of classifying a cancer as being correlated with a greater amount of expression of **an erbB-3 gene** as compared to a control comprising measuring the level of expression of the erbB-3 gene in a sample from a subject diagnosed with cancer and comparing the level of expression to the level of expression in a sample form a control subject**.**

The claims are drawn to a broad genus of erbB-3 genes of unknown structure and function.

The specification discloses that the present invention relates to a DNA segment having a nucleotide sequence of an erbB-3 gene in which that nucleotide sequence encodes the amino acid sequence of an erbB-3 protein or a unique portion thereof. The sequence of this portion of an erbB-3 amino acid sequence differs in at least one amino acid residue from the amino acid sequence encoded by any other DNA segment. This portion of an erbB-3 amino acid sequence includes at least about 4 to 6 amino acids which are sufficient to provide a binding site for an antibody specific for this portion of the erbB-3 polypeptide (p. 7, lines 7-16). The specification further discloses that it will be understood by on skilled in the art of genetic engineering that in relation to production of erbB-3 polypeptide products, the present invention also includes DNA segments having DNA sequences other than those in the present examples that also encode the amino acid sequence of the polypeptide product of an erbB-3 gene (p. 8, lines 10-15). The present invention further relates to a DNA segment having a nucleotide sequence that encodes an amino acid sequence differing in at least one amino acid from the amino acid sequence of human erbB-3, or a unique portion thereof, and having greater overall similarity to the amino acid sequence of human erbB-3 than to that of any other polypeptide (p. 8, lines 27-32). A DNA segment can encode an amino acid sequence having substantially the function of the human erbB-3 polypeptide (p. 9, lines 3-5). Finally the specification discloses the predicted amino acid sequence of human erbB-3 polypeptide in Figure 4. The specification does not disclose any other erbB-3 genes as broadly encompassed in the claims.

The art (see Kraus et al, PNAS, 1989, 86:9193-9197, IDS) teaches the amino acid sequence of erbB-3 expressed by the human erbB-3 gene (Figure 3), however this sequence does not provide an adequate representative number of species to support adequate written description for the broad genus of erbB-3 genes as encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of "an erbB-3 gene". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure,

formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an

invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an erbB-3 gene, per Lilly by structurally describing representative erbB-3 genes or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe an erbB-3 gene useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses a human erbB-3 amino acid sequence in Figure 4, this does not provide a description of the broadly claimed erbB-3 genes that would

satisfy the standard set out in Enzo because the specification provides no structural features coupled to functional characteristics.

Further, the specification also fails to describe an erbB-3 gene by the test set out in Lilly because the specification describes only a human erbB-3 gene in Figure 4. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of an erbB-3 gene that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed method uses, it also fails to adequately describe the method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 43-46, 51, 52, 55, and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemoine et al I (Br J Cancer, December 1992, 66:1116-1121), as evidenced by Prigent et al (Oncogene, July 1992, 7:1273-1278).

Lemoine et al I teach a method comprising measuring the level of erbB-3 protein in breast cancer biopsies from human breast cancer patients, and comparing it to the level of erbB-3 protein measured in normal breast tissue biopsies from women with no

cancer, wherein erbB-3 was overexpressed in approximately 22% of the breast cancer cases, hence these cases are correlated with a greater amount of erbB-3 expression as compared to the normal controls (abstract; p. 1116, col. 2 through p. 1117; p. 1119-1120). Lemoine et al I used immunohistochemistry to detect erbB-3 protein using polyclonal antibodies that specifically recognize erbB-3, wherein the antibodies are described by Prigent et al (p. 1117, col. 2), and wherein the antibodies would be labeled for detection in immunohistochemistry.

As evidenced by Prigent et al, the polyclonal antibodies bind the cytoplasmic domain of erbB-3 (abstract; p. 1273, col. 2). Prigent et al teach that the antibodies recognized erbB-3 and did not cross-react with other proteins (p. 1273, col. 2), therefore it is expected the antibodies used by Lemoine et al I do not bind EGFR or erbB-2.

6. Claims 43-45, 51-53, 55, 57, and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Rajkumar et al (J of Pathology, 1993, 170:271-278), as evidenced by EP 0 444 961 A1, Plowman et al, published September 4, 1991.

Rajkumar et al teach a method comprising measuring the level of expression of erbB-3 protein (c-erbB-3) in samples from human patients with tumors of the gastrointestinal tract, and comparing the level of expression to the level of expression in normal samples using immunocytochemistry, wherein the antibody is detectable (p. 272; p. 274), wherein the tumor samples had higher levels of erbB-3 staining (greater amount of expression) than normal tissue (p. 274-276, Figure 3). Rajkumar et al teach

using monoclonal antibody RTJ1 and polyclonal antibodies to detect erbB-3 protein in the samples, wherein the antibodies bind a cytoplasmic domain, or intracellular domain, of erbB-3 (abstract; p. 272; p. 274). Given the method taught by Rajkumar et al comprises identical steps to the claimed method, the method taught by Rajkumar et al would necessarily classify cancer as being correlated with a greater amount of expression of erbB-3 protein as compared to a control. Further, it is expected that a subset of the polyclonal antibodies that bind to erbB-3 would not bind to EGFR or erbB-2, given sequence differences (as evidenced by EP 0 444 961 A1, Plowman et al, published September 4, 199, Figure 3) between the three different proteins that would yield erbB-3-specific antibodies.

The reference does not specifically teach that the monoclonal antibody used for immunocytochemistry does not bind EGFR or erbB-2. However, the claimed antibody appears to be the same as the prior art antibody, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 43-45, 51, 52, 55, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prigent et al (Oncogene, July 1992, 7:1273-1278) in view of Lemoine et al II (Gut, October 1992, 33:1297-1300).

Prigent et al teach a method of measuring the level of expression of erbB-3 (c-erbB-3) protein in normal tissues, including gastrointestinal tract, using polyclonal antibodies that bind the cytoplasmic domain of erbB-3 (abstract; p. 1273, col. 2; p. 1274, col. 2; Table 1). Prigent et al used immunocytochemistry to stain for erbB-3 protein expression which requires labeling the antibody (p. 1278, col. 1). Prigent et al teach that the antibodies recognized erbB-3 and did not cross-react with other proteins (p. 1273, col. 2), therefore it is expected the antibodies did not bind EGFR or erbB-2. Prigent et al teach that their study of determining erbB-3 expression in normal tissues provides the basis for assessing the expression levels of erbB-3 in human tumors (p. p. 1277, col. 2).

Lemoine et al II teach that erbB-3 (c-erbB-3) is known to be over-expressed in specific tumors of the gastrointestinal tract, and is over-expressed in oesophageal, stomach, and colorectal cancers (p. 1298, col. 1), and suggests using immunocytochemical staining to examine normal pattern of protein distribution (p. 1297, col. 2). Given Lemoine et al II teach erbB-3 is known to be overexpressed in specific

tumors, it is inherent that a comparison had to be made to normal tissue to determine that overexpression is occurring in the tumors.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the step of measuring levels of erbB-3 protein expression in tumor samples for comparison to the normal tissue expression because Prigent et al specifically suggests doing so. One would have been motivated to add the step of measuring levels of erbB-3 protein expression in tumor samples for comparison to the normal tissue expression in order to determine if erbB-3 is overexpressed in tumor tissues, as Lemoine et al II teaches. One of ordinary skill in the art would have a reasonable expectation of measuring levels of erbB-3 protein expression in tumor samples for comparison to the normal tissue expression to determine erbB-3 overexpression because Prigent et al demonstrate successful methods of measuring erbB-3 protein expression in human tissue samples, and Lemoine et al II teach that overexpression of erbB-3 in tumors is known.

8. Claims 43, 51-54, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajkumar et al (J of Pathology, 1993, 170:271-278) in view of EP 0 444 961 A1, Plowman et al, published September 4, 1991, IDS.

Rajkumar et al teach a method comprising measuring the level of expression of erbB-3 protein (c-erbB-3) in samples from human patients with tumors of the gastrointestinal tract, and comparing the level of expression to the level of expression in normal samples using immunocytochemistry, wherein the antibody is detectable (p.

272; p. 274), wherein the tumor samples had higher levels of erbB-3 staining than normal tissue (p. 274-276, Figure 3). Rajkumar et al teach using monoclonal antibody RTJ1 and polyclonal antibodies to detect erbB-3 protein in the samples, wherein the antibodies bind a cytoplasmic domain, or intracellular domain, of erbB-3 (abstract; p. 272; p. 274), as set forth above.

Rajkumar et al does not teach that the monoclonal or polyclonal antibodies bind the extracellular domain of erbB-3.

Plowman et al teach the sequence of erbB-3 (HER3) (Figure 1) and compare its sequence to that of EGFR and erbB-2 (neu) disclosing the extracellular and intracellular domains (Figure 2). Plowman et al teach making HER3 monoclonal and polyclonal antibodies specific to an epitope of HER3 (p. 7, section 5.3), and teach using the antibodies diagnostically and to assess HER3 expression immunologically by immunoassays such as radioimmunoprecipitation or ELISA (p. 6, section 5.1.3 and p. 7, section 5.4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use polyclonal or monoclonal antibodies to the extracellular domain of erbB-3 in the method taught by Rajkumar et al because the sequence of erbB-3 and methods of making antibodies to it are known. One would have been motivated to make and use antibodies to the extracellular domain of erbB-3 in the method of Rajkumar et al because Plowman teach such antibodies can be made and used for immunoassays. One of ordinary skill in the art would have a reasonable expectation of success using antibodies that bind the extracellular domain of erbB-3 in

the method of Rajkumar et al because methods of making antibodies to known protein sequences and using antibodies in immunoassays are routine and conventional practice.

9. Claims 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajkumar et al (J of Pathology, 1993, 170:271-278) and EP 0 444 961 A1, Plowman et al, published September 4, 1991, as applied to claims 43, 51-54, 56 above, and further in view of Brotherick et al (Cancer Immunol Immunother, 1995, 41:280-286).

Rajkumar et al and Plowman et al (the combined references) teach a method comprising measuring the level of expression of erbB-3 protein (c-erbB-3) in samples from human patients with tumors of the gastrointestinal tract, and comparing the level of expression to the level of expression in normal samples using immunocytochemistry, wherein the antibody is detectable, wherein the tumor samples had higher levels of erbB-3 staining than normal tissue, and using monoclonal or polyclonal antibodies that bind the intracellular or extracellular domain of erbB-3 as set forth above.

The combined references do not teach that the antibody is bound to a support.

Brotherick et al teach measuring levels of erbB-3 protein in breast cancer biopsies using anti-erbB-3 antibodies bound to bead solid support and flow cytometry (abstract; p. 281-284).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute flow cytometry using antibodies bound to solid support to measure levels of erbB-3 in place of immunohistochemistry in the

method of the combined references because Brotherick et al teach flow cytometry is a method for measuring levels of erbB-3 in biopsy samples. One would have been motivated to use flow cytometry in order provide a more precise measurement or level of erbB-3 positive cells, as demonstrated by Brotherick et al in Figures 2 and 3. One of ordinary skill in the art would have a reasonable expectation of success using flow cytometry, which uses antibodies bound to solid support, to measure levels of erbB-3 in the method of the combined references because flow cytometry is a known and successful method of measuring erbB-3 levels in patient biopsies. One of skill in the art could have substituted one known erbB-3 measuring assay for another, the flow cytometry for the immunohistochemistry, and the results of measuring levels of erbB-3 to determine greater expression would have been predictable.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 43-45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28 and 29 of **U.S. Patent No. 5,916,755**. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant application and US patent are claiming common subject matter. The claims of both the instant application and US Patent are drawn to methods comprising measuring the amount or level of expression of erbB-3 protein in a biological sample from a subject and comparing it to the amount or level in a normal sample, wherein a higher amount or level in the biological sample indicates overexpression of erbB-3, further comprising correlating the overexpression of erbB-3 to the presence of a neoplastic condition.

11. All other rejections recited in the Office Action mailed July 6, 2007 are hereby withdrawn.

12. **Conclusion:** No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642